REMARKS/ARGUMENTS

Status of the Claims

Claims 1 and 4-16 were last examined. Claims 7-12 are withdrawn from consideration. Claims 13-16 are canceled herein. Claim 1 is amended to replace the transitional phrase "comprising" with the more limited scope transitional phrase "consists essentially of" with reference to the composition of the nucleic acid probes of the array. Each probe has the nucleic acid sequence of on of the sequences in the sequence listing. Applicants assert that no new matter is presented by these amendments and respectfully request entry of the same.

Objections to the Specification

In paragraph 2, the disclosure is objected to because the title of the invention is not descriptive. The specification has been amended to provide a title that is clearly indicative of the invention to which the claims are directed.

In paragraph 3, the disclosure is objected to because of informalities. The specification has been amended to correct the references to "mouse genes" and "the mouse genome" on page 17 lines 27-29 and page 25 lines 9-11 and to replace the reference to SEQ ID Nos 1-982,914 on page 25 line 9 with the correct numbers, SEQ ID Nos. 1-688,466.

In paragraph 4, the disclosure is objected to because it contains an embedded hyperlink. The specification has been amended to remove the embedded hyperlink on page 19, line 7. Withdrawal of these objections is respectfully requested.

Rejections under 35 U.S.C. § 101 should be withdrawn.

In paragraph 6, claims 1, 4-6, and 13-16 are rejected under 35 U.S.C. § 101 as allegedly lacking utility. The Examiner asserts that the claimed invention is not supported by

either a specific and substantial asserted utility or a well established utility. Applicants respectfully disagree.

First, the Office Action alleges that the claimed invention lacks a "specific utility" because the disclosed uses of the nucleic-acids array of the rat genome "are generally applicable to any nucleic acid."

Section 101 of Title 35 of the United States Code states that for an invention to be patentable it must be useful:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Following the requirements of the Utility Examination Guidelines published at 66 FR 1092, Jan. 5, 2001, superseding the Revised Interim Utility Examination Guidelines that were published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136 (2000); and correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67 (2000), a rejection based on lack of utility should not be imposed if the claimed invention has either a (1) well-established utility or the applicant has (2) asserted a specific and substantial utility that is credible. An assertion that the claimed invention is useful for a particular purpose is sufficient provided that the assertion would be considered credible by a person of ordinary skill in the art.

The claimed invention has a substantial utility:

In the utility guidelines training materials "substantial utility" is defined as "a utility that defined a 'real world' use". Several uses for the collection of probes are disclosed in the specification. For example, on page 17, lines 20-21, of the specification the following use for the arrays are disclosed: "simultaneous measurement of relative gene expression levels for at least 20,000 rat genes."

It is clear that at the time of filing of the present application it was well known to one of skill in the art that an array of probes to detect expression products from the rat genome had the utility of measuring gene expression profiles. This is demonstrated by numerous peer reviewed articles describing real world applications of the Affymetrix Rat Genome U34 array set. As noted by the Examiner, the U34 array set is an earlier product made available by Affymetrix that provides a probe array comprising a plurality of probes to rat expression products. One such article, Stuart et al., PNAS 98:5649-5654 (2002), has been provided herewith as Appendix A. Stuart et al. reports analysis of gene expression changes during kidney organogenesis in rat using the Affymetrix Rat Genome U34A array. One of sill in the art would have recognized the utility of the claimed array in the method described by Stuart et al.

This use defines a substantial real world use for the claimed invention. The claimed invention is not a single probe or probes to a single gene but probes to a collection of more than 20,000 rat genes. Simply because the invention includes nucleic acid probes, the Examiner appears to require a demonstrated association between one of the genes and a "useful phenotype". Applicants respectfully assert that this is a misapplication of the utility guidelines and a misunderstanding of the claimed invention.

Applicant is not claiming a single probe to a single gene. What Applicant is claiming is an array of 699,466 twenty-five base probes to individually, reproducibly and accurately interrogate the expression level of a collection of more than 20,000 rat genes and to do so simultaneously. Each probe sequence is selected because they met specified criteria that allow them to function together in a single assay. Each probe is part of a probe set (typically 11 probes) that is designed to hybridize specifically to a known or predicted expression

product from a rat gene. The probes in the probe set are designed so that the probe set recognizes a particular target without cross hybridization to non-target transcripts that may be present in the sample. Probes are also selected for inclusion in a probe set so that they function together to give optimal performance under a specified set of hybridization conditions.

In particular, the commercial embodiment of the claimed invention, the GENECHIP Rat 230 Array, has been used by researchers in studies to identify genes that are regulated by maternal care in a rat model. *See*, Weaver et al., PNAS 103: 3480-3485 (2006), a copy of which is provided herewith as Appendix B. The study identified more than 900 genes in the hippocampus of adult rats that are significantly altered in expression as a function of maternal care early in life. The results suggest epigenetic reprogramming in response to maternal care that results in long-term changes to gene expression patterns. In addition to this one example study, there are more than 100 peer reviewed publications describing studies performed using the Rat 230 array. Applicants believe that the utilities asserted for the claimed invention are substantial and that this is demonstrated by the real world uses for which the array has been applied by those of skill in the art.

The claimed invention has a specific utility:

The training materials define a "specific utility" as "a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention." A utility need not be unique to a claimed invention and can be shared by a class of inventions. Ex parte Fisher at 1028. The outcome of this analysis depends on what the broad class of the invention should be. Applicants assert that the broad class for comparison should be all possible collections of 699,466 twenty-five base nucleic

acids probes. There are 4^{25} different possible 25 base sequences so the number of possible combinations of 699,466 different 25 mers is very large. Clearly not all possible sets of probes would have the asserted utility of the presently claimed set of probes. These probes are all perfectly complementary to rat sequences and more specifically to rat genes. Further, the probes are complementary to regions of the genome that are present in rat mRNA and in particular the probes are complementary to the antisense RNA generated when mRNA is amplified by transcription amplification. Other sets of probes could be selected that would be complementary to and capable of measuring the level of a collection of messenger RNA from rats, but for any given message there are many different probes that could be selected. Not all sets of 699,466 probes would have the same utility as the claimed set of probes.

What Applicants are claiming is not an individual genomic sequence, but a collection of 699,466 genomic sequences that functions as a set of probes to interrogate the expression level of more than 20,000 rat genes under selected amplification and hybridization conditions. The specification asserts a credible, substantial and specific utility for the claimed invention, making the rejection of the claims under 35 U.S.C. §101 improper.

The rejection of the claims under the enablement provision of 35 U.S.C. §112 is a corollary of the finding of lack of utility and Applicants request that it be reversed for the same reasons set forth in Applicants' arguments above regarding the rejection under 35 U.S.C. § 101.

Rejections under 35 U.S.C. § 112 should be withdrawn.

In paragraph 8, claims 1, 4-6, and 13-16 are rejected under 35 U.S.C. § 112 as allegedly failing to comply with the written description requirement. Claim 1 has been amended to replace the transitional phrase "comprising" with the more limited scope transitional phrase "consists essentially of" with reference to the composition of the nucleic

acid probes of the array. The full length probes are no longer than 25 bases in length and have the sequence of one of the sequences in the sequence listing without additional flanking sequence. They may be attached to the array via a linker molecule.

Rejections under 35 U.S.C. § 102 should be withdrawn.

In paragraph 10, claims 1, 4, 13, and 15 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Affymetrix Rat Genome U34 Set (Jan 2001). Applicants respectfully traverse this rejection. What is being claimed is a particular set of probe sequences and the collection of probes present on the Affymetrix Rat Genome U34 array set is not identical to the collection of probes of the claimed array. Many of the probes that are included in the presently claimed array of probes are not present on the U34 array. For example, the presently claimed array has 699,466 different probes while the U34 set has only 420,907 different probes so there are at least 278,000 probes that are present on the claimed array that are not present on the U34 set.

The Affymetrix GeneChip Rat Genome U34 array is the closest prior art to the presently claimed array, that is sold commercially as the Affymetrix GeneChip Rat Genome 230 2.0 array, but there are important differences. First, the database of sequences used to design each array is different. The presently claimed array was designed using sequences selected from GenBank, dbEST and RefSeq. The sequence clusters were created from the UniGene database (Build 99, June 2002) and then refined by analysis and comparison with the publicly available draft assembly of the rat genome from the Baylor College of Medicine Human Genome Sequencing Center (June 2002). The U34 array was designed from Build 34 of the UniGene Database (Build 34) with additional full-length sequences from GenBank release 110 (1/21/99 and 2/19/99). Second, the U34 uses 16 pairs of oligonucleotide probes

to measure the transcript level of each gene while the presently claimed array uses 11 probe pairs per transcript. Third, the presently claimed array has probe sets representing approximately 31,000 transcripts, 28,700 of those being well-substantiated rat genes. The U34 interrogates approximately 24,000 transcripts. Fourth, the presently claimed array has 699,466 probes while the U34 has 420,907 probes (see the revised sequence listing provided with U.S. Patent application No. 09/954,427, now abandoned), so there are 278,559 probes on the presently claimed array that are not present on the U34 array set.

Applicants provide the following example to demonstrate that the probes of the presently claimed array differ in sequence from the probes of the U34 array set. Probe sets for the gene peroxisome proliferator activated receptor gamma, PPARG, were identified on both the 230 array set and the U34 array set. The 11 probes in the PPARG probe set on the 230 array are shown in Table 1 and the 16 probes for the PPARG probe set on the U34 array are shown in Table 2:

Table 1. PPARG perfect match probes from Rat 230 array

	Probe sequence 5'-3'	SEQ ID NO
1	AGGGAGTTCCTCAAAAGCCTGCGGA	148497
2	GCGGAAGCCCTTTGGTGACTTTATG	400259
3	GTGACTTGGCCATATTTATAGCTGT	503379
4	ATTATTCTCAGTGGAGACCGCCCAG	206208
5	GTGAAGCCCATCGAGGACATCCAAG	501323
6	GGACATCCAAGACAACCTGCTGCAG	421548
7	TGTTCGCCAAGGTGCTCCAGAAGAT	653470
8	GATTGTCACAGAGCACGTGCAGCTA	373783
9	GGAGACAGATATGAGCCTTCACCCT	425495
10	GAAAAGTCCCAGTCGCTGACAAAGT	284224
11	GTGTTCCTTCTATCGATTGCACTAT	519997

Table 2: PPARG perfect match probes from U34 array

	Probe sequence 5'-3'	SEQ ID NO
1	GCCTCCCTGATGAATAAAGATGGAG	
2	GATGGAGTCCTCATATCAGAGGGAC	
3	AGTCCTCATATCAGAGGGACAAGGA	
4	ATTCATGACCAGGGAGTTCCTCAAA	
5	TGACCAGGGAGTTCCTCAAAAGCCT	
6	AGGGAGTTCCTCAAAAGCCTGCGGA	148497
7	TCCTCAAAAGCCTGCGGAAGCCCTT	
8	GCGGAAGCCCTTTGGTGACTTTATG	373783
9	AAGCCCTTTGGTGACTTTATGGAGC	
10	CTTTGGTGACTTTATGGAGCCTAAG	
11	GTGAAGTTCAATGCACTGGAATTAG	
12	AGATGACAGTGACTTGGCCATATTT	
13	TTTATAGCTGTCATTATTCTCAGTG	
14	AGCTGTCATTATTCTCAGTGGAGAC	
15	TCATTATTCTCAGTGGAGACCGCCC	
16	ATTCTCAGTGGAGACCGCCCAGGCT	

Of the 11 probes to PPARG that are included in the presently claimed array only two, SEQ ID NO 148497 and SEQ ID NO 400259, are also found on the U34 array. In addition, two of the probes in the U34 array show significant regions of overlap with probes in the claimed set.

SEQ ID NO 503379 GTGACTTGGCCATATTTATAGCTGT
U34 12 AGATGACAGTGACTTGGCCATATTT

SEQ ID NO 206208 ATTATTCTCAGTGGAGACCGCCCAG
U34 14 AGCTGTCATTATTCTCAGTGGAGAC

The remaining 7 probes in the 11 probe PPARG probe set are not found in the U34 set. This gene was selected at random and is representative of the differences between the probes of the two arrays. The U34 array therefore fails to teach each and every limitation of the present claims.

In paragraph 11, claims 1, 4, 6, 13, 14, and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Gunther et al. (1985). Gunther et al. teaches a Southern blot of rat genomic DNA and is cited as containing probes containing the entire rat genome as a collection of restriction fragments. As amended, the presently claimed array differs from the teaching of Gunther et al. at least in the requirement that the probes are all 25 bases and each sequence is a separate probe.

In paragraph 12, claims 13-16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Brennan (U.S. Patent No. 5,474,796). Claims 13-16 have been canceled herein making this rejection moot.

Rejections under 35 U.S.C. § 103 should be withdrawn.

In paragraph 14, claims 5, 6, 14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Affymetrix Rat Genome U34 Set (Jan 2001) in view of Fodor et al. (IDS: U.S. Patent No. 6,309,822). Claims 14 and 16 have been canceled herein. Claim 5 is directed to array of claim 1 where the probes of claim 1 are attached to beads and different probe sequences are attached to different beads. Claim 6 is directed to the array of claim 1 where the probes are attached to a single contiguous solid support. The probes of the U34 array are separated onto three non-contiguous chips.

To establish a *prima facie* case of obviousness the prior art reference or references must teach or suggest all the claim limitations. Neither the U34 array set nor Fodor et al. teach or suggest the specific set of probes claimed in independent claim 1. As discussed above, the claimed set of probes does not entirely overlap the set of probes on the U34 in sequence and there are at least 278,000 probes that are present on the claimed array that are

not present on the U34 array. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

In paragraph 16, claims 1, 4-6, and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rat UniGene Build 99 Set (Jun 2002) in view of Fodor et al. (IDS: U.S. Patent No. 6,309,822). The Unigene database is cited as teaching the sequences of rat genes and ESTs and, as indicated in the specification, the claimed probe sequences are complementary to genes and EST clusters from this build of the database. Fodor et al. is cited as teaching that arrays may comprise up to 1,000,000 different oligonucleotide probes that are preferably 20 to 25 nucleotides in length. The Examiner is of the opinion that, given the sequence information provided in Unigene build 99 and the information provided in Fodor about the length and number of probes, it would have been obvious to select the particular 699,466 sequences claimed. From this it would appear to follow that any set of twenty-five base probes targeting the transcripts of Unigene build 99 would be equivalent to the selected set of probes. Applicants respectfully disagree. The 699,466 probes selected for inclusion in the array are a unique set of probes that were carefully selected to function as a set on an array for gene expression analysis. The choice of probe sequence depends on numerous criteria, such as hybridization behavior, secondary structure, propensity for cross hybridization to other probes in the set, target preparation methods and manufacturing considerations. Not all sets of 699,466 twenty-five base probes from Unigene build 99 would have the function of the claimed set. There are likely other sets of probes that could have been selected to have similar function, but the specific claimed set of probes was chosen from the many possible sets of probes to obtain an array that has optimal performance given our current understanding of probe, array and assay performance

In paragraph 15, claims 1, 4-6, and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rat UniGene Build 34 (1998) in view of Fodor et al. (IDS: U.S. Patent No. 6,309,822). As discussed above, Fodor et al. in combination with Unigene build 99 fails to anticipate the presently claimed specific set of probes. Unigene build 34 contains at best a subset of the information contained in Unigene build 99 and the combination of Unigene build 34 with Fodor et al. fails to make the presently claimed invention obvious for at least the same reasons.

CONCLUSION

For these reasons, Applicants believe all pending claims are now in condition for allowance. If the Examiner has any questions pertaining to this application or feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5768.

Respectfully submitted,

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Attachments: Appendix A: Stuart et al. 2001
Appendix B: Wheatley et al. 2006

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